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EXAMINER	
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ART UNIT	PAPER NUMBER
1636	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/769,902	GOODMAN ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 28 May 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☒ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1-12*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☒ Other: *Note the attached PTO-982.*

Continuation of 3. Applicant's reply has overcome the following rejection(s): Rejection of claims 1-12 under 35 USC 112, first paragraph, as adding new matter. Rejection of claims 1-12 under 35 USC 112, second paragraph.

Continuation of 5. does NOT place the application in condition for allowance because: The rejection of claims 1-12 as failing to meet the enablement requirement of 35 U.S.C. §112, first paragraph was maintained in the Final Office Action mailed 24 February 2003 (Paper No. 14). In response Applicant cites several articles and provides a Declaration under 37 C.F.R. §1.132 from Dr. Martin Blank to support enablement for the claimed subject matter. Each of these will be addressed in turn. First, however, it is important to establish the scope of the claimed subject matter. Although the specification mentions that the claimed method can be used to introduce an exogenous insulin gene, the disclosure does not contemplate the treatment of any specific disease using the method. Therefore, it is assumed that applicant is claiming a method of which comprises gene therapy of any and all conditions. This assumption is supported by Applicant's statement on page 14 of Paper No. 11 that, "the specification by mentioning gene therapy, inherently means that it is a method of treating any genetic disease." Thus, enablement for the full scope of the claimed subject matter requires enablement for gene therapy of any and all genetic diseases in any and all subjects, wherein a subject is an animal of any species which is in need of therapy.

Applicant again argues that the references cited by the examiner to establish a prima facie case of non-enablement are outdated and that gene therapy is generally enabled due to several recent advances in the field. To support this assertion, Applicant cites the following articles:

Jindal et al. (2001) Int. J. Exp. Diabetes Res. 2 :129-138, which teaches delivery of preproinsulin into an immunocompromised mouse using an AAV vector ; Ye et al. (1999) Science 283:88-91, which teaches delivery of erythropoietin to mice and a rhesus monkey using an AAV vector system; Edelberg et al. (1998) J. Clin. Invest. 101:337-343, which teaches gene transfer of a b2 adrenergic receptor into a murine neonatal cardiac transplantation model; Edelberg et al. (2001) Heart 86:559-562, which teaches gene transfer of a b2 adrenergic receptor into pig hearts; Rosenger et al. (1999) Ann. Surg. 230:466-470, which teaches a 6 month follow-up of a phase I clinical trail of VEGF gene therapy of coronary artery disease; Navarro et al. (1999) Gene Therapy 6:1884-1892, which teaches gene transfer of reporter genes into neurons using an adenovirus; Park et al. (2000) Blood 96:1173-1176, which teaches gene transfer of human factors VIII and IX into mice using a lentiviral vector; Kon et al. (1999) J. Gene Med. 1:186-194, which teaches gene transfer of insulin into diabetic mice; Steiner et al. (1998) Hum. Gene Ther. 9:747-755, which teaches inhibition of tumor cell growth by expression of a c-myc antisense construct from a retrovirus construct; Zhonghua et al. (2001) The First People's Hospital of Shanghai 30:198-201, which teaches Hsp70 regulated expression of a target gene in a tumor cell; Madio et al. (1998) J. Magn. Reson. 8:101-104, which teaches induction of endogenous hsp70 expression using MRI-guided focused ultrasound; Okano et al. (2001) Bioelectromagnetics 22:408-418, which teaches the effect of static magnetic fields on blood pressure in rabbits; Tofani et al. (2001) Bioelectromagnetics 22:419-428, which teaches the effect of static and ELF magnetic fields on tumor growth and apoptosis; DiCarlo et al. (1998) Bioelectromagnetics 19:498-500, which teaches the effect of electromagnetic fields on anoxic chick embryos; Kapturczak et al. (2001) 1:245-258, which provides a review of gene therapy of type 1 diabetes with an emphasis on AAV gene transfer; and Collateral Therapeutics, Inc. (Public Release, 2001), which teaches that germ cells were unaffected following intracoronary delivery of an adenoviral vector.

Although some of the teachings contained in the cited art are demonstrative of the slow progress towards effective therapy that is characteristic of the gene therapy art, the art does not support Applicant's contention that gene therapy is generally enabled for any and all genetic diseases in any and all subjects.

The experiments of Jindal et al. were performed in immunocompromised animals and thus do not account for the immune responses that have severely hindered development of gene therapy treatments (discussed in previous office actions).

Ye et al. clearly demonstrates the unpredictability of extending results obtained in one mammalian species to other species of mammals. Experiments performed in mice showed no diminution in induced EPO expression at 6 months after gene transfer (see especially Figures 1 and 2 and the captions thereto), while induced EPO-expression was undetectable in non-human primates 4 months after gene transfer for unknown reasons (see especially Figure 4 and the caption thereto, and the first paragraph in the right column on page 90).

Edelberg et al. (1998) summarizes their findings this way, "these studies demonstrate that the basal rate of the heart can be enhanced by local delivery of exogenous genes which can be used to improve our understanding of the regulation of cardiac automaticitiy...these investigations also provide an integrated experimental approach for identifying candidate genes and developing local delivery approaches for maximizing/prolonging effects of these candidate genes...the above approaches may eventually be useful in the potential development of both transient molecularly mediated and stable cellular-based cardiac pacemakers" (final paragraph in the left column of page 342). Edelberg et al. thus teaches that the method disclosed therein might one day be useful in the potential development of a therapeutic method. Likewise, Edelberg et al. (2001) teaches that b2 adrenergic receptor gene transfer into pig hearts transiently increased heart rate and characterizes the findings this way, "these studies showed that the basal rate of the heart can be enhanced by local intravascular delivery of exogenous genes. These investigations may provide a foundation for developing novel therapeutics for cardiac chronotropic disorders" (page 562, second full paragraph). This is far from teaching an enabled gene therapy method applicable to a genetic disease in any subject.

Although clinical trial of Rosengart et al. shows some trend toward therapeutic effect, the findings are equivocal due to the small number of patients in the study and, as pointed out by Rosengart et al., "the results are too preliminary to substantiate efficacy" (see especially the first paragraph of the "Discussion" on page 469). Given the high degree of unpredictability regarding obtaining therapeutic efficacy using gene therapy approaches, as established in previous office actions, the skilled artisan would not view the teachings of Rosengart et al. as enabling for a method of gene therapy in all subjects.

Navarro et al. teaches that adenovirus mediated gene transfer can provide reporter gene expression in neurons in vivo. However, expression is clearly reduced over time (see especially Figures 4 and 5, and the captions thereto) and Navarro provides no guidance with regard to how the method described therein can be used to effectively treat a disease. In fact, Navarro et al. teaches only that the vector and method disclosed therein, "offers the possibility of transferring 2potentially therapeutic genes into neurons within brain areas

affected by various neurodegenerative diseases" (page 1890, fourth paragraph). Given the high degree of unpredictability regarding obtaining therapeutic efficacy using gene therapy approaches, the skilled artisan would not view the teachings of Navarro et al. as enabling for a method of gene therapy in all subjects.

Park et al. teaches gene transfer of human factors VIII and IX into mice using a lentiviral vector. However, in contrast to applicant's assertion that the teachings support the general enablement of gene therapy for genetic diseases, Park et al. exemplifies many of the problems encountered in developing a gene therapy approach to the treatment of any given disease. Park teaches that expression of factor VIII was inhibited by an immune response against the protein in immunocompetent mice (see especially the Abstract). Although factor IX expression was better than factor VIII, Park et al. clearly teaches, "[f]urther improvements in lentiviral vectors will likely be required to achieve therapeutic levels of hFIX at a dose that is considered safe" (page 1175, final sentence in column 1). Thus, Park et al. teaches that the vectors available as of August 2000 remained inadequate for predictable gene therapy. Park et al. further teaches, "to produce therapeutic levels of coagulation factors, techniques need to be developed to promote cell cycle progression in a safer, nonsurgical manner, such as the use of growth factors" (paragraph bridging pages 1175 and 1176). Therefore, Park et al. clearly teaches that much work remains before gene therapy is enabled for the treatment of hemophilia, let alone any and all genetic conditions in any and all subjects.

Kon et al. teaches gene transfer of insulin into diabetic mice. Although some therapeutic effect is obtained in mice, Kon et al. teach, "the present study suggests that insulin gene transfer into skeletal muscle mediated by naked DNA could provide some therapeutic benefit in diabetes mellitus, further substantial improvements will be required before this approach can be seriously considered for clinical use" (paragraph bridging columns 1 and 2 on page 193; emphasis added). Thus, the teachings of Kon et al. regarding the therapeutic benefit of the method disclosed therein in the treatment of diabetes mellitus are equivocal and clearly indicate the need for further investigation.

Although Steiner et al. teaches some therapeutic effect of c-myc antisense expression in mouse tumor models, Steiner et al. teaches that the findings do not generally support a method of gene therapy of prostate cancer in mammals, stating, "[t]he effectiveness of prostate specific retroviral gene therapy in humans who have advanced prostate cancer remains to be determined" (page 754).). Thus, the skilled artisan, exemplified by the authors of Steiner et al., would not consider the methods set forth therein as broadly enabled for therapeutic effect in all subjects.

Zhonghua et al. teaches Hsp70 regulated expression of a reporter gene in a tumor cell. However, Zhonghua et al. do not teach a therapeutic effect and given the high degree of unpredictability regarding obtaining therapeutic efficacy using gene therapy approaches, the skilled artisan would not view the teachings of Navarro et al. as enabling for a method of gene therapy in all subjects and for any and all genetic diseases.

Madio et al., Okano et al., Tofani et al. and DiCarlo et al. teach various effects of electromagnetic fields on biological systems. The teachings do not, however, contemplate gene therapy and therefore do not address the basis of the enablement rejection, which is the unpredictability of achieving therapeutic effect in the treatment of any and all genetic diseases in an and all subjects using gene therapy.

Kapturczak et al. provides a review of gene therapy of type 1 diabetes with an emphasis on AAV gene transfer. Although Kapturczak et al. is generally optimistic about the future of AAV vectors in gene therapy, the authors also acknowledge that there is much work to be done in order to develop an effective gene therapy for type 1 diabetes. Kapturczak et al. teaches, "[a]t present, many questions exist that must first be addressed in animal models", including: which gene or genes will be most effective in preventing and/or delaying islet cell transplant rejection; will genes for allograft rejection prevent recurrent autoimmunity and vice versa; and how safe will islet cell immunomodulatory therapy be in terms of overall physiology. Thus Kapturczak et al. teaches that there is much to be learned before gene therapy is enabled for type 1 diabetes in any animal let alone any and all subjects.

Finally, Applicant cites Collateral Therapeutics, Inc., which teaches that germ cells were unaffected following intracoronary delivery of an adenoviral vector. Again, therapeutic effect was not demonstrated.

Taken as a whole, the art of record indicates that, at the time of filing, limited therapeutic effects had been observed in experimental models of a handful of genetic diseases. Again, it must be emphasized that the claimed method is not limited to gene therapy of any of the diseases for which some evidence of therapeutic effect is shown. The claims encompass gene therapy of many intractable diseases and genetic diseases which comprise multiple genetic components or for which the genetic component is unknown. This is pointed out by Kapturczak et al. who teaches that one of the problems encountered in developing gene therapy "was the finding that most diseases are polygenic, involving multiple genetic factors. An example is the case of type 1 diabetes where at least 18 separate chromosomal regions have been associated with genetic susceptibility to the disorder" (page 248, third paragraph). Therefore, even if vector and promoter systems had been perfected by the time the instant application was filed (which the art of record clearly indicates is not the case) the skilled artisan would not be able to practice the claimed method the vast majority of genetic diseases without engaging in undue experimentation to overcome the barriers to therapeutic effect that are unique to each disease, such as identifying a therapeutic gene.

Applicant has submitted a Declaration by Dr. Martin Blank, wherein Dr. Blank states his belief that the teachings of the instant disclosure and relevant art as of the filing date of the application would enable one of ordinary skill in the art to conduct a working in vivo experiment to practice the claimed invention such that a sustained therapeutic result is obtained. In paragraph 6 of the Declaration, Dr. Blank outlines steps involved in introducing an EMRE containing gene into a patient and applying an electromagnetic field. The statements in the Declaration have been fully considered but are not found persuasive because they do not address the general unpredictability of obtaining therapeutic effect using gene therapy techniques. That is, the method steps set forth summarize what would be readily apparent to one of skill in the art but do not address the intricacies of immune response against vectors and transgenes and problems of promoter shut-down, etc., which have hindered the development of therapeutic methods using gene therapy techniques. Furthermore, the teachings of the declaration are not enabling for the full scope of the claims which, as pointed out above, encompass a method of gene therapy for any and all genetic diseases.

In support of enablement based on in vitro data, Applicant also points to MPEP §2164 which states that the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. However, given the vast scope of conditions that Applicant purports to treat according to the claimed method, it stands to reason that the limited number of examples provided in the specification and cited art cannot be correlated with the full scope of the claims. For example, the claims encompass gene therapy of schizophrenia, yet there is nothing in the record that would suggest successful therapy of schizophrenia.

Finally, Applicant again criticizes the art cited by the examiner, which was published in or before 1997, as not representative of the state of the art at the time of filing. However, as Applicant is aware, the Examiner's burden is to establish a prima facie case of nonenablement. Clearly the art cited by the examiner establishes that case. Although Applicant has cited more recent art, the teachings of each of the articles cited by Applicant have been considered and an explanation of why the art fails to overcome the rejection has been provided. As the teachings of the art of record fail to provide enablement for the full scope of the claimed subject matter, the claims stand rejected under 35 U.S.C. §112, first paragraph..

JAMES KETTER
PRIMARY EXAMINER